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Chemical Research at the Institut für Strahlenchemie, Mülheim
A. Paul Schaap
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red blood cells	phytochrome	deoxyribonucleic acid
olefin radical cation	vesicles	inositol hexaphosphate (IHP)
photochemistry	hemoglobin	photochemical disinfection of water

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

The Institut für Strahlenchemie (Radiation Chemistry) which is located in Mülheim, FRG, was founded in 1958 as a unit attached to the Max-Planck-Institut für Kohlenforschung (Coal Research). The Institute for Radiation Chemistry is involved in research in a variety of areas including: (1) chemical effects of ultraviolet radiation, γ-rays, and high-energy electrons on organic and biological systems; (2) new methods of synthesis; (3) organic and organometallic photochemistry; and (4) theoretical chemistry. A specific major research

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effort of the institute involves the radiation chemistry of deoxyribonucleic acid and model compounds.

Described in this report are recent results from various research projects in progress at the institute. Schaffner and co-workers have been involved in a study of photochemical reactions of β,γ-unsaturated ketones. The photoisomerization of a bicyclo[3.2.2]nonanaphthalene yields a strained tricyclic semibullvalene type product. Catalytic reversal of this reaction in the dark can be effected at ambient temperature. Schaffner has pointed out that this cycle represents a model for chemical light energy storage. Schaffner has also been involved in a detailed study of the photophysical properties of biliverdin, a substrate closely related in structure to the plant photoreceptor, phytochrome.

The chemistry of ethers and acetals under ^{60}Co γ-radiolysis and UV irradiation has been studied by Schulte-Frohlinde and von Sonntag. Kinetics of the reactions were monitored by pulse conductivity methods using electron pulses from a 2.8 MeV van de Graaff generator.

Research by Nicolau on the use of vesicles to deliver inositol hexaphosphate (IHP), an allosteric effector of hemoglobin, to red blood cells (RBC) may result in procedures for dramatically increasing the oxygen release capacity of RBC. Potential applications include an improved O_2 supply to tissues under low O_2-partial pressures in air such as at high altitudes. Preliminary experiments with rats have shown that incorporation of IHP into the RBC enables the rats to adapt to reduced O_2 partial pressures.

CHEMICAL RESEARCH AT THE INSTITUT FÜR STRAHLENCHEMIE, MULHEIM

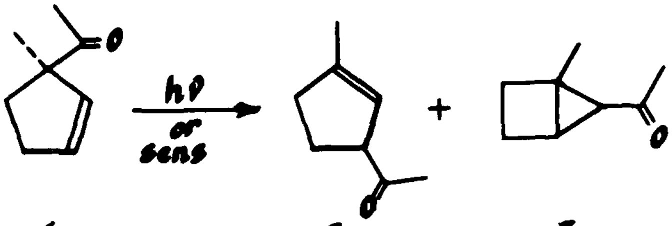
The Institut für Strahlenchemie was founded in 1958 as a unit attached to the Max-Planck-Institut für Kohlenforschung (Coal Research). The former institute is financed by the Max Planck Gesellschaft (MPG), a research organization whose institutes are established to carry out scientific work for the benefit of the public. The activities of the Max Planck Institutes are principally in the fields of natural science and the humanities. The institutes in particular devote their attention to new problems which are not sufficiently developed for university research or problems that are less suited for the university because of the scope and structure of the research. The MPG operates 50 institutes, research units, and project groups distributed throughout the Federal Republic of Germany and West Berlin. Approximately 80% of the funds used by the MPG comes from the Federal Government and the state governments.

The Max-Planck-Institut für Kohlenforschung in Mülheim was founded in 1912. The first director of the institute was Prof. Franz Fischer and it was during the period of 1920 to 1940 that the Fischer-Tropsch synthesis was developed. This process, which converts carbon monoxide and hydrogen derived from coal into hydrocarbons, has been important in the past, but with the energy crisis it will receive increasingly more attention in the future. A change in research emphasis came with the appointment of Prof. Karl Ziegler in 1943 as director. A study of organometallic chemistry was initiated which eventually led to the development of the Ziegler catalysts. These catalysts, for which Ziegler was awarded the Nobel Prize for chemistry in 1963, are used for the conversion of olefins into plastics. In 1974 products valued at DM4,000,000 ($2M) were manufactured by processes developed at this institute. It is, therefore, not surprising that the Institute for Coal Research is unique among Max Planck institutes in that it is an autonomous foundation which is financed almost entirely from the income of its research activities. The present director of this institute is Prof. Günther Wilke.

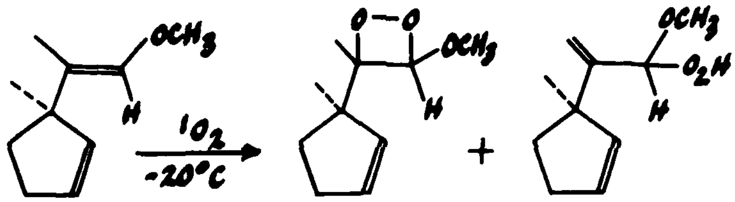
The Institute for Radiation Chemistry is involved in a wide variety of research areas including: (1) chemical effects of ultraviolet radiation, γ-rays, and high-energy electrons on organic and biological systems; (2) new methods of synthesis; (3) organic and organometallic photochemistry; and (4) theoretical chemistry. A specific major research effort of the institute involves the radiation chemistry of deoxyribonucleic acid (DNA) and model compounds. The institute has a staff of approximately 170 persons of whom more than 30 are senior scientists with an additional 50 guest scientists. The 3 directors of the institute are Prof. Oskar Polansky, Prof. Dietrich Schulte-Frohlinde, and Prof. Kurt Schaffner. The institute is extremely well-equipped with modern instruments for chemical research. Two 3 MeV van de Graaff electron accelerators are available for pulse radiolysis investigations. A cobalt-60 source is also used for radiation chemistry experiments. Described below are but a few examples of the elegant research being conducted at this institute.

The mechanism of the photosensitized rearrangement of β,γ-unsaturated ketones has been a continuing area of study for Schaffner and his collaborators. There are two characteristic photoreactions of most β,γ-enones: (1) a triplet sensitized oxadi-π-methane rearrangement which is assumed to occur from the lowest-lying $^3\pi,\pi^*$ state and (2), an allylic 1,3-acyl shift which occurs upon direct irradiation and which is commonly ascribed to a $^1n,\pi^*$ state. However, Schaffner and other

investigators have recently pointed out that all of the available evidence can also be reconciled with a 1,3-shift which occurs from a short-lived T_2 state of n,π* character. Schaffner's group has recently studied the reactivity of the triplet excited state of 3-acetyl-3-methylcyclopentene (1) generated by the thermal decomposition of high energy peroxides, 1,2-dioxetanes 5a,b. The product distribution obtained was compared with that from direct and triplet-sensitized photolysis. At 25°C, direct irradiation of 1 gave principally the 1,3-acetyl shift product 2, whereas triplet sensitization by acetone favored the oxadi-π-methane rearrangement to 3 (Table 1).



1 2 3



4 5a,b 6a,b

$$\underline{5a,b} \xrightarrow{80°C} \underline{1} + \underline{2} + \underline{3} + HCO_2CH_3$$

Table 1. Direct and Triplet-Sensitized Photolysis of 1 at 25°C. Quantum Yields of Conversion and Product Formation

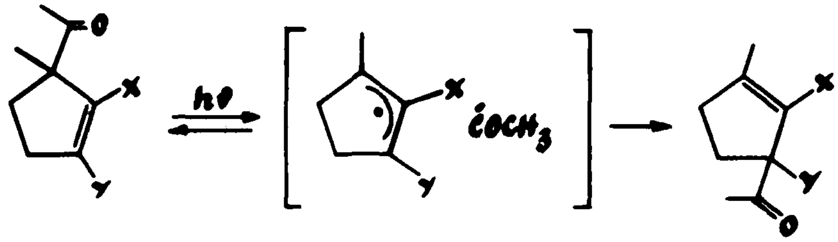
excitation	Φ_{-1}	Φ_2	Φ_3	Φ_2/Φ_3
direct	0.65	0.20	0.04	5.0
sensitized	0.70	0.015	0.46	0.033

Photooxygenation of enol ether 4 was used to produce the 2 diastereomeric dioxetanes 5a,b (12% each) and the hydroperoxides 6a,b (75%). Thermolysis of dioxetanes 5a,b at 80°C generated singlet excited 1 as evidenced by chemiluminescence which accompanied the reaction. The chemiluminescence spectrum was found to match the fluorescence spectrum of 1. Rearranged ketones 2 and 3 in a ratio of 1.9:2.7 were obtained as products from the thermolysis of the dioxetanes, further indicating the formation of excited states of 1. Determinations of the chemiluminescence quantum yield indicated that the decomposition of the dioxetanes yielded predominantly triplet excited states. A comparison of the product distribution of 2 and 3 at 80°C (Table 2) indicates a striking difference in the relative yields with the mode of excitation. The acetone-sensitized reaction of 1 gave 3 in a much higher proportion than the decomposition of dioxetanes 5a,b. Schaffner has indicated that these results require the existence of two triplet states of 1 with differing reactivities. The novel observation is that these triplet states are apparently not populated equally by the thermal chemiexcitation and the photosensitized modes. Molecular orbital calculations by Polansky and Dr. G. Olbrich are in agreement with the above results and indicate that there are two triplet states for 1 with predominantly $^3n,\pi^*$ and $^3\pi,\pi^*$ character and an energy separation of no more than 12 kJ/mol.

Table 2. Rearrangement Products of 1 at 80°C

starting material	excitation	product 2, %	product 3, %	ratio of 2/3
1	direct, λ 313 nm, in acetonitrile	15.3	5.6	2.73
1	sensitized, λ 254 nm, in acetone	2.3	74.4	0.031
5a,b	thermal decomposition (20 min) in acetonitrile	1.9	2.7	0.70

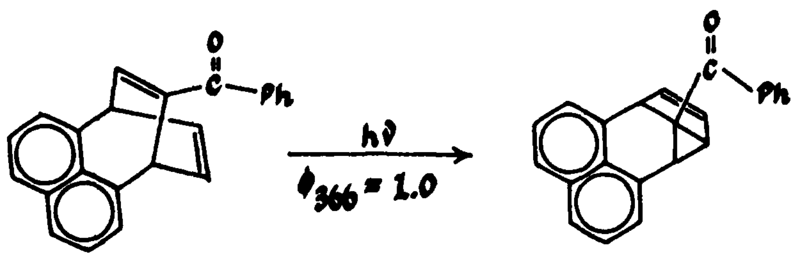
The mechanism of the excited state rearrangement of β,γ-unsaturated ketones (such as 7 to 8) has also been addressed by Schaffner and co-workers through the use of photo-CIDNP experiments. The mechanism of this allylic 1,3-acyl shift has been a subject of considerable debate in the literature. Among the mechanisms that have been considered are: (1) a concerted process involving the $^1n,\pi^*$ state; (2) a radical pair mechanism proceeding predominantly from the $^3n,\pi^*$ state; and (3) for β,γ-unsaturated ketones with a lowest-lying $^3\pi,\pi^*$ state, reaction from a short-lived T_2 state. Schaffner has found that photo-CIDNP effects from 7a-c exhibited an intriguing temperature dependence in the range of -60 to +140°C. These results are interpreted in terms of an allylic shift that proceeds via radical pairs originating from both the S_1 and T_2 states depending on the reaction temperature.



7a $X = Y = CH_3$
7b $X = CH_3$, $Y = H$
7c $X = Y = H$

8

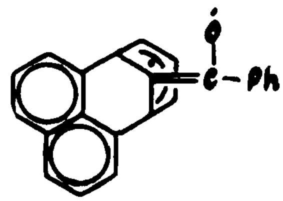
An interesting study of the photoisomerization of the bicyclo[3.2.2]nonanaphthalene 9 to give the tricyclic semi-bullvalene-type product 10 has been carried out by Schaffner's group. This photoreaction can be effected by either direct irradiation with 316 or 366 nm light or with triplet sensitizers of greater than 60 kcal. Deuterium labeling experiments have been carried out to elucidate the mechanism. Irradiations were conducted in 2-methyltetrahydrofuran matrices and electron spin resonance and infrared spectra were recorded at 77 K. This work has provided the first direct evidence of the intermediacy of a biradical intermediate (or a category of biradical intermediates) in di-π-methane photochemistry and confirms the stepwise mechanism for the photorearrangement of barrelenes that was originally postulated by Prof. H.E. Zimmerman (Univ. of Wisconsin).



9 10

It has also been observed that the interconversion of 9 $\rightleftarrows$ 10 can be effected thermally without the intervention of light. The thermal transformation of 9 → 10

represents the first example of a ground-state counterpart of a di-π-methane photo-rearrangement. A thermally equilibrated mixture of 98.8% 9 and 1.2% 10 was obtained when either of the two components was heated in benzene at 220°C. A stepwise mechanism that is in accord with the results of deuterium labeling studies has been suggested for this reaction. The intermediacy of biradical 11 is proposed.



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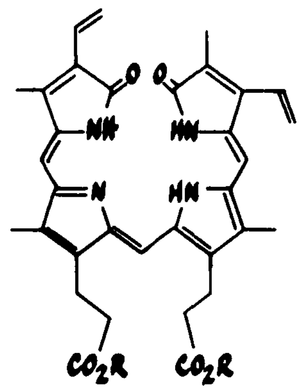
The rearrangement of 10 → 9 can also be carried out at ambient temperature in the presence of strong electrophiles; e.g., treatment of 10 in chloroform with trimethylsilyl trifluoroacetate resulted in clean conversion to 9. Schaffner has pointed out that the sequence of the photochemical rearrangement of 9 → 10 which occurs with 100% efficiency and the catalytic reversal of 10 → 9 in the dark represents a model of a cycle for chemical light energy storage which can be conducted without detectable destruction of the reactants.

Dr. Sylvia Braslavsky, Schaffner, and co-workers have recently been involved in a thorough study of the photophysical properties of biliverdin (12a) and its dimethyl ester 12b. Biliverdin is a precursor of the yellow bile pigment bilirubin in heme catabolism and has received the increasing attention of several research groups in the last few years because of its close structural relationship to the chromaphoric group of phytochrome. Phytochrome is the plant photoreceptor or chromoprotein which triggers the photomorphogenic processes in plants. This group has been particularly careful in the preparation and purification of 12b by high pressure liquid chromatography and has carried out its subsequent studies on a sample of 12b of unequivocally established homogeneity. There apparently has been considerable difficulty in the purification of this compound by other groups, the result of which has been some erroneous data in the literature. The fluorescence of the biliverdin dimethyl ester 12b has been studied under a variety of conditions. Freshly prepared solutions of 12b in ethanol showed fluorescence maxima at 710 and 770 nm (ambient temperature). The maxima of monoprotonated 12b at 77 K were shifted to 725 and 806 nm. The acid effect was found to be reversible by neutralization with base. It was observed that when a neutral solution was kept standing in the dark at ambient temperature, or when an acidic solution was neutralized by base, an additional fluorescence maximum at 500 nm was produced. This appearance of a new blue fluorescence upon "aging" of a solution of 12b may well be the source of some of the confusion in the literature. The structure of the species that results in this new fluorescence is not known, but the nucleophilic addition of solvent to 12b appears a likely cause.

Additional studies on 12b and its XIII α-isomer by this group have employed high-field magnetic resonance spectroscopy (300 MHz) with double resonance decou-

pling and nuclear Overhauser effect (NOE) experiments. Another technique used by this group to investigate the conformation of the isomeric biliverdins in solution was ethyl (S)-(-)-lactate-induced circular dichroism at ambient temperature.



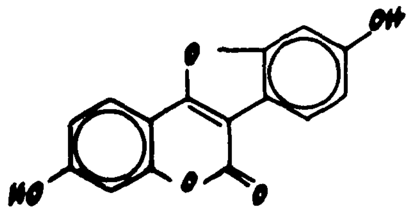
12a, R=H
12b, R=CH_3

These results all provide evidence for a helical conformation for these substrates in solution. A ^{1}H-NMR kinetic study of a derivative of biliverdin has shown that the barrier to interconversion of the helical conformations is 42 kJ/mol in the range of 205 to 195 K. Work is continuing in this very important area with studies of the fluorescence and solvent-induced circular dichroism of bilirubin. Recent results have shown the existence of two or more forms of bilirubin dimethyl ester involving either or both *syn-anti* dipyrromethenone and lactam-lactim equilibria. Schaffner and his collaborators have found that the relative population of these forms is strongly influenced by the nature of the solvent and by temperature.

Prof. Otto S. Wolfveis (Univ. of Graz, Austria) and Schaffner have collaborated on a study of the solvent and acidity dependence of the photophysical properties of coumestrol. Coumestrol (13), which exhibits strong estrogenic activity, is found in clover and other plants as a result of fungal diseases. Other investigators have identified coumestrol as the agent responsible for transient or permanent infertility (clover disease) produced in sheep which graze on coumestrol-enriched leguminosae pastures. Wolfveis and Schaffner have carried out the first detailed study of the solvent and acidity-dependent fluorescence properties of coumestrol. They have found that in neutral, non-aqueous solvents emission stems from the uncharged S_1 state. However, in aqueous solutions of 13, five species have been identified: the neutral form, the mono- and dianions, and the mono- and dications.

Schulte-Frohlinde and his collaborators are concerned primarily with the reactions of substrates under ^{60}Co γ-radiolysis and pulsed electron radiolysis. Model compounds selected for study are designed to provide further information about the mechanism of radiation-mediated deoxyribonucleic acid (DNA) damage. The formation and structure of 1,1-dialkoxyalkene radical cations in aqueous solu-

tion have recently been studied by Schulte-Frohlinde. The structures of the radical cations have been elucidated by *in situ* electron spin resonance (ESR) experiments. The reactions are initiated by hydrogen atom abstraction from substrates such as 14 by triplet excited acetone, HO• radicals, or $SO_4^{\cdot -}$ radicals upon UV irradiation of acetone, H_2O_2 or $S_2O_8^{2-}$, respectively. Subsequent heterolytic dissociation yields the radical cation 15 and the leaving group. Schulte-Frohlinde has found that the radical cations are best observed at pH <5. Radical cations have been generated from both open-chain and cyclic acetals with various leaving groups such as Cl, Br, or CH_3CO_2 groups β to the acetal CH moiety. Open-chain radical cations such as 15 were found by ESR to exist in Z,E-conformations as evidenced by two sets of a_{δ}^{H} couplings. The kinetics of the reactions have been studied by pulse conductivity methods using 2.8 MeV electron pulses of 1 ms duration from the van de Graaff generator.



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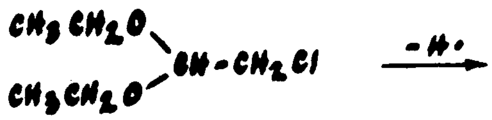

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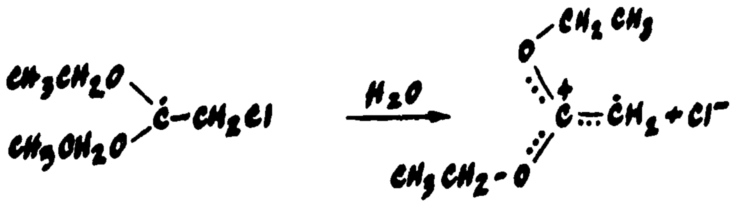

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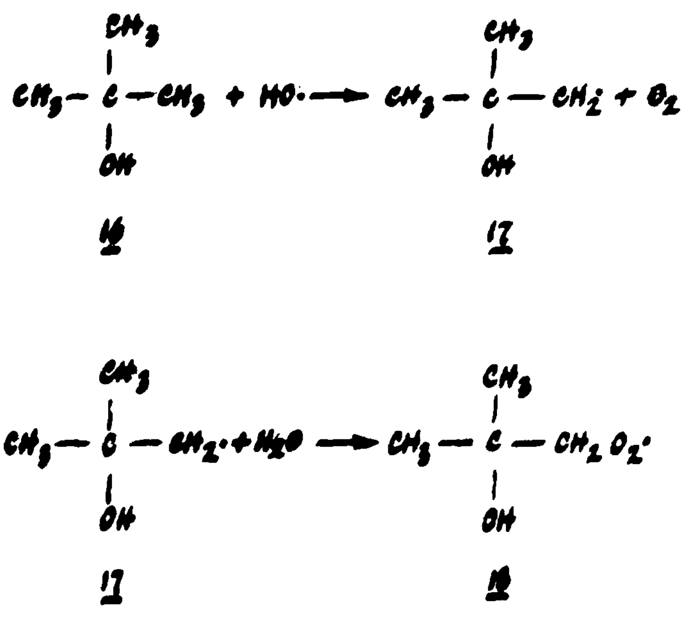
Schulte-Frohlinde and H. Görne. in an investigation of the photophysics of stilbene and 4-halogenated stilbenes have obtained evidence for an upper excited triplet pathway for the *trans* to *cis* photoisomerization of these compounds. They have employed a frequency quadrupled Nd laser with excitation at 265 nm for their studies. They have measured in various solvents the triplet lifetime and the quantum yield of triplet formation for these compounds as a function of temperature. A comparison of these data with the quantum yields of direct *trans* to *cis* photoisomeriza-

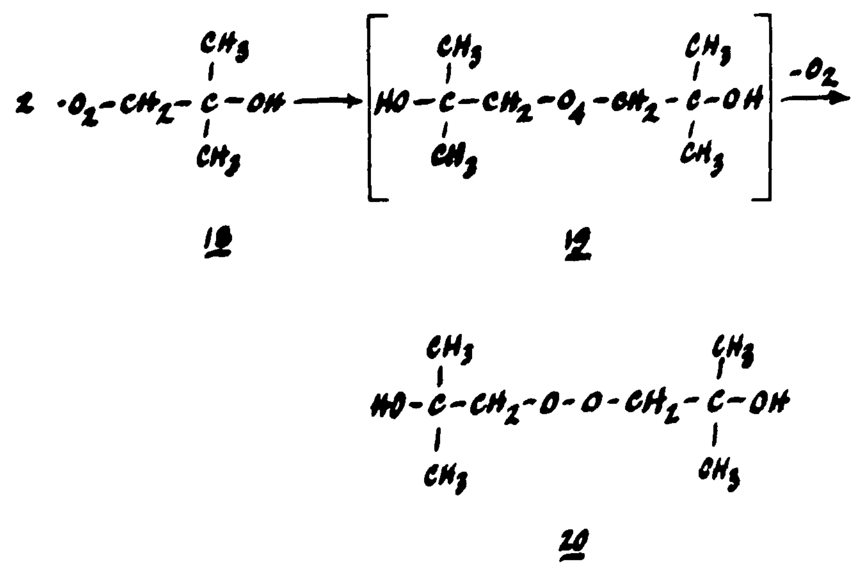
tion and of the fluorescence of the *trans* isomer as a function of temperature has provided evidence for two different triplet pathways in addition to the singlet pathway. The two triplet pathways are followed mainly in different temperature and viscosity ranges.

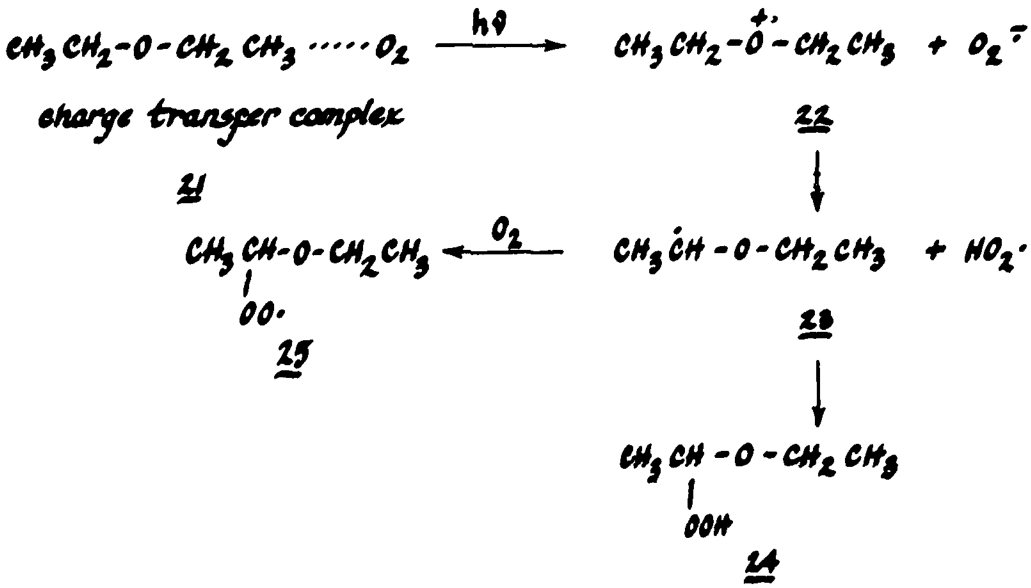
In studies directed toward providing additional insight into the mechanism of radiation-induced DNA chain breaks, Dr. Clemens von Sonntag and co-workers have recently been involved in research on the reactions of hydroxyl radicals with various substrates. Recently they have investigated the hydroxyl radical-induced oxidation of 2-methyl-2-propanol (16) in oxygenated aqueous solution. The various products from the reaction were characterized and pulse radiolysis techniques were employed to study the kinetics of the reaction. ^{60}Co γ-radiolysis of aqueous solutions generate as the primary reactive species hydroxyl radicals (HO•), solvated electrons (e^-_{aq}), and hydrogen atoms (H•). HO• radicals attack alcohol 16 by preferentially abstracting carbon-bound hydrogen atoms, generating the 2-hydroxy-2-methylpropyl radical 17. Subsequent addition of oxygen to 17 at a diffusion controlled rate forms the corresponding peroxy radical 18. Von Sonntag has isolated several products from this reaction, one of which is the peroxide 20. A mechanism for the formation of 20 has been proposed and involves the intermediacy of tetroxide 19. A pulse radiolytic investigation of this reaction has been carried out using the 2.8 MeV van de Graaff generator with electron pulses of 1 μsec duration and doses of 2.5 to 20 J/kg. The kinetics of the reaction were followed by monitoring transient conductivity changes produced immediately after the pulse. Additional information concerning the mechanisms of these oxidation reactions has been obtained by deuterium labeling experiments.



Von Sonntag and co-workers have also been interested in the radiation chemistry of ethers. They have studied the UV photolysis at 254 nm of the diethyl ether-oxygen charge-transfer complex 21. Among the major products that are ob-

served from this reaction are H_2O_2, ethyl acetate, acetaldehyde, and ethanol. Von Sonntag indicated that all of the products can be explained on the basis of a mechanism which involves electron transfer from the ether to oxygen as the primary process upon irradiation. Elimination of a proton from the radical cation 22 to give $HO_2\cdot$ and 23 with subsequent cage combination of these radicals yields the hydroperoxide 24. The major source of the observed products, however, appears to be the peroxy radical 25 formed by the reaction of oxygen with 23. Experiments are also in progress in which 185 nm excitation is used. Radiation chemistry using this short wavelength light appears likely to be an increasingly active area of research at the institute.

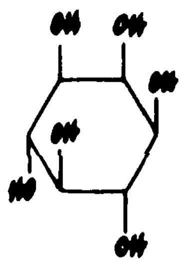




Dr. Claude Nicolau and Prof. Klaus Gersonde (Rheinisch-Westfalische Technische Hochschule, Aachen, FRG) have collaborated to develop a procedure for dramatically increasing the O_2 release capacity of red blood cells (RBC) in the circulating blood by up to 280% with the possibility of greatly improved O_2 supply to tissues. Experiments have also shown that these modifications of RBC can last over a significant period of time and suggest improved procedures for the storage of blood.

At a normal O_2 partial pressure of 100 mm in the lungs, approximately 95% of the hemoglobin (Hb) is saturated with O_2. Therefore, under physiological conditions the O_2 loading of RBC proceeds efficiently. Less efficient, however, is the O_2 release in the peripheral bloodstream where O_2 has to be dissociated from the oxygenated Hb against a relatively high O_2 partial pressure. Consequently, only about 25% of the oxygenated Hb may be deoxygenated with about 75% being returned to the lungs with the veinous blood. Therefore, as Nicolau and Gersonde point out, a major fraction of the O_2 which is bound to Hb is not released and could be available as a source of O_2.

Other workers had shown in the early 1970s that polyphosphates such as *myo*-inositol hexaphosphate (IHP) decrease the O_2 affinity of Hb (or increase the O_2 release capacity). *myo*-Inositol (26) is a hexahydroxycyclohexane which occurs naturally and is widely distributed in microorganisms, higher plants, and animals.



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In plants it is found as the fully phosphorylated derivative, phytic acid. IHP is the strongest known allosteric effector of hemoglobin decreasing dramatically the O_2 affinity. The interaction of IHP and isolated Hb had been studied extensively, but because water-soluble polyphosphates such as IHP cannot permeate the erythrocyte membrane in order to bind to Hb, there had been no studies of IHP with intact red blood cells.

Nicolau and Gersonde have found that the interaction of RBC with lipid vesicles with encapsulated IHP leads to an irreversible incorporation of IHP in RBC. Lipid vesicles consisting of one or more concentric lipid bilayers enclosing an aqueous compartment can transfer the water-soluble and membrane-impermeant IHP by a process of fusion of the outer lipid layer of the vesicle with that of the RBC membrane with concomitant delivery of the encapsulated IHP into the RBC. These workers have employed in their studies unilamellar vesicles with a diameter of less than 500 Å which have entrapped 0.19 M IHP solution in isotonic saline buffer. The bilayer structure consists of a lipid mixture of phosphatidylcholine, phosphatidylserine, and cholesterol in an 8:2:7 molar ratio, respectively. The vesicles

are formed by ultrasonic dispersion with separation of the unilamellar vesicles from the larger multilamellar vesicles by ultracentrifugation.

To take advantage of the IHP benefits for the treatment of blood, Nicolau and Gersonde indicate that it would be necessary to separate the RBC from other blood constituents, since the vesicles will also be incorporated by the lymphocytes or will interact with serum lipoproteins resulting in loss of the entrapped IHP. Thus, the incorporation of IHP into RBC is only possible *in vitro*; i.e., extracorporal. After washing, the IHP-loaded RBC can be resuspended in the blood plasma and the treated blood can be retransfused to the animal.

^{31}P nuclear magnetic resonance spectra have shown that the concentration of free IHP is extremely small in the cell. Further, the IHP and Hb are quantitatively bound with a one to one stoichiometry. These workers have described an experiment which clearly demonstrates the enhancement of the O_2 release capacity of IHP-loaded RBC. Fusion of 41-day old human RBC with IHP vesicles increased the O_2 half-saturation pressure from 15.5 to 58 mm Hg at 37°C indicating that 56% of the intercellular Hb had bound IHP. Under physiological conditions, for example, in transport to the brain, non-treated 46-day old RBC exhibit an O_2 release of 17% of the total O_2 transport capacity. However, RBC which have transformed 56% of its Hb into the lower affinity structure by binding with IHP show an O_2 release of 47% of the total O_2 transport capacity.

Nicolau and Gersonde have used scanning electron microscopy to investigate the effects of IHP on the shape and membrane properties of RBC. Electron micrographs of the RBC just after fusion with the vesicles show small bumps on the cell surface of the RBC. However, after resuspension in blood plasma and healing at 37°C, the RBC return to their normal shape with the loss of the bumps. It has also been shown that ATP levels do not change significantly after IHP incorporation. Further, experiments indicate that the fluidity of the cell membrane remains unaltered by the IHP.

No back transport of IHP across the erythrocyte membrane has been detected. Experiments over a 40-day period show no significant decrease in the concentration of the IHP bound to Hb, a result of the fact that RBC have no hydrolytic enzymes with IHP specificity. It has also been discovered that CO_2 transport by RBC is enhanced by bound-IHP. Unlike RBC, which when stored at 4°C in stabilizer solutions undergo a progressive increase in O_2 affinity and depletion of ATP, the IHP-treated RBC exhibit an enhanced O_2 release capacity which remains unchanged over an extended period.

Nicolau and Gersonde point to several potential applications of erythrocytes with incorporated IHP, one of which involves improved O_2 supply to the tissues under low O_2-partial pressure in air such as at high altitude. Preliminary experiments with rats have shown that incorporation of IHP into the RBC enables the rats to adapt to reduced O_2-partial pressures.

Polansky, H. Karpf, and M. Zander have observed the first example of a photochemically induced addition of maleic anhydride to a polycyclic aromatic hydrocarbon of the type that contains a peripheral cisoid C^4-unit. Because molecular orbital calculations by Polansky had shown that chrysene was not expected to undergo a Diels-Alder reaction in the ground state, but should react photochemically in the S_1 state, Polansky and co-workers have recently been investigating the photochemical addition of maleic anhydride to chrysene. Novel experiments were carried

out in which xenon was used as an external heavy atom perturber to increase the intersystem crossing of chrysene S_1 to T_1. A decrease of 40% in the yield of the photoadduct was taken as evidence for the involvement of the S_1 state of the reaction.

Finally, it is a personal pleasure to report that Prof. Günther O. Schenck, who was instrumental in the establishment of the Institute for Radiation Chemistry and who with his collaborators substantially developed the field of photosensitized oxidation, is actively involved in a new photochemical project. Schenck is involved in the design of photochemical reactors for use in disinfecting water. Various geometries of the photoreactors and a variety of ultraviolet light sources are being considered. Calculations of doses, degermination capacities, and costs for the degermination are being carried out.